REMARKS

Claims 1-13, 15, 16 and 18-30 are pending in the application.

Claims 14 and 17 have been canceled.

Claims 1-9 and 18-29 have been withdrawn.

Claim 10 has been amended. Support for the amendment can be found on page 46, lines 2-4 and in Figures 9 and 10.

New dependent claim 31 has been added.

No new matter has been added.

Rejections Under 35 USC § 103

Further to the arguments presented in the Response filed July 6, 2010, Applicants present the following additional arguments.

Applicants first note that claim 10 has been amended to recite that the regenerated cementum and the regenerated alveolar bone have a periodontal ligament between them. The presence of a periodontal ligament between the cementum and the alveolar bone is a non-obvious difference between the instant invention and the cited prior art. As stated by Dr. Kurihara in the attached Declaration dated August 5, 2010, the skilled artisan understands that ankylosis is defined as the fusion of the cementum and alveolar bone with obliteration of the periodontal ligament (see page 40 of Clinical Periodontology 8th edition (1996), Fermin A. Carranza et al., eds., W.B. Saunders Company, Philadelphia; reference submitted herewith). Thus, this difference is both unique and unexpected over the prior art.

Applicants next note that there are a large number of growth factors that are expressed in the peripheral nervous system or the periodontal tissue, although generally little is known about

the growth factors that are expressed in both the peripheral nervous system and the periodontal tissue. Consequently, while there may be a somewhat limited number of neurotrophic factors compared to a fairly large number of growth factors, there was no compelling reason for a skilled artisan to select neurotrophic factors for experimentation, especially a particular group of neurotrophic factors.

For example, IL-6 is expressed in the peripheral nervous system and the periodontal tissue. The IL-6 superfamily contains neurotrophic factors. IL-6 itself protects the neuronal cell from death by oxidative stress in the peripheral nervous system (see Fujishita et al. (2009) Cell Mol Neruobiol 29:1121-1129 and Fujita et al.(2009) Glia 57:244-257; attached hereto). While IL-6 has not been examined for its effects on regeneration of periodontal tissue, it is well known as a pro-inflammatory cytokine which is involved with the progression of the destruction of periodontal tissue caused by periodontis (see Scheres et al. (2010) J Periodontol 45:262-270; attached hereto). This fact alone would discourage, i.e. teach away from, the skilled artisan targeting neurotrophic factors.

Based on this example, one of skill in the art would not have had a reasonable expectation of success in accomplishing periodontal regeneration by using any growth factor. Because so little information was known about the action of growth factors in the periodontal tissues at the time of filing, and considering the fact that many growth factors are known but the information as to their function in the periodontal tissues is unclear, the skilled artisan could not have expected to obtain a positive result as was found using the neurotrophic factors of brain-derived neurotrophic factor, nerve growth factor, neurotrophin-3, and neurotrophin-4/5.

It is known that periodontal tissue regeneration works as a cascade, which means the sequential regenerative process in which many growth factors and cells are involved. In the cascade, adequate growth factors and cells work at adequate timing, amount and duration to regenerate tissue. But in general the difference observed depends on whether experiments are done in vitro or in vivo because of the metablolizing process of any target drug. That is, in vitro studies do not always equate to in vivo studies.

BDNF is known to play a role in the survival and differentiation of central and peripheral neurons in vitro. So BDNF has been implicated in pathophysiological mechanisms of many diseases of the nervous and immune system, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), neuropathy, pain, allergic bronchial asthma (BA) and neurotrophic keratitis. Yet despite some clinical trials performed to reveal the beneficial effect of BDNF in ALS patients, no statistically significant survival effect of BDNF in ALS patients was revealed. This fact indicates that the results of in vitro studies are not always reflected in in vivo studies, and there was no reason to believe that any results from applying BDNF in vitro would necessarily hold true when BDNF was applied in an in vivo system.

Furthermore with respect to BDNF, applicants point out that the combination of this neurotrophic factor and hyaluronic acid provided unexpectedly improved results. Figure 1, attached, presents results showing that the combination of BDNF and a tissue absorbing material made of high molecular weight-hyaluronic acid (HMW HA) is statistically significantly improved as compared to the use of HMW-HA alone or BDNF with poly(lactic acid-co-glycolic acid) (PLGA). That is, the BDNF/HMW-HA group was statistically improved for cementum growth at the level of $P<0.05$ for BDNF concentrations at 5 μg/mg, 500 μg/mg and 2000 μg/mg compared to HMW-HA alone and for generating new bond at concentrations of 50 μg/mg and 2000 μg/mg. Comparing both new cementum length and new bone growth for BDNF/HMW-HA to that obtained for BDNF/HPLGA, the results obtained for BDNF/HMW-HA are statistically significant at the level of $P<0.01$. This provides evidence that not any support material can provide the results obtained.

In conclusion, the Examiner has not made a proper case of prima facie obviousness. Consequently, Applicants respectfully request removal of the rejections and allowance of the claims.

Conclusion

In view of the above, all of the claims are submitted as defining non-obvious, patentable subject matter. Removal of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D., Reg. No. 47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Enclosures: Dr. Kurihara Declaration dated August 5, 2010
Clinical Periodontology 8th edition (1996), Fermin A. Carranza et al., eds., W.B. Saunders Company, Philadelphia
Fujishita et al. (2009) Cell Mol Neruobiol 29:1121-1129
Fujita et al.(2009) Glia 57:244-257
Scheres et al. (2010) J Periodontol 45:262-270
Figure 1